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(54) Title: METHODS AND COMPOSITIONS FOR PREVENTING AND TREATING URINARY TRACT DISORDERS

(57) Abstract: The present invention relates to methods, compositions, devices and kits for the prevention and treatment of urinary tract disorders in mammals, including, but not limited to, urinary incontinence of any etiology, urinary hesitancy, fibrosis of the urinary tract, urinary dribbling, cystitis of any etiology, urinary frequency, and bladder cancer. The present invention provides methods for preventing and treating urinary tract disorders in mammals by administration of a therapeutic compound to mucosal membranes in the lower urinary tract of the mammal. The present invention also provides devices for administering a therapeutic compound to mucosal membranes in the lower urinary tract of the mammal.

METHODS AND COMPOSITIONS FOR PREVENTING AND TREATING URINARY TRACT DISORDERS

Field of the Invention

The present invention relates to compositions, methods, devices and kits for the prevention and/or treatment of urinary tract disorders and diseases. The present invention further relates to compositions, methods, devices and kits for application of therapeutic compounds to the mucosa of the lower urinary tract.

Background of the Invention

Urinary tract disorders are among the most common medical disorders in mammals. The "urinary tract" consists of the various organs of the body that produce, store, and get rid of urine. These include the kidneys, the ureters, the bladder and the urethra.

The lower urinary tract is composed of the bladder, which is surrounded by the detrusor muscle, and the urethra. These structures form a functional unit that functions to store and void the urine in the case of the bladder with the urethra acting to control and convey the urine. Contraction of the detrusor muscle initiates voiding.

When functioning properly, the urinary tract is a marvel of efficiency. Throughout every 24-hour period, it thoroughly cleanses approximately 200 quarts of fluid, returning most of it to the circulatory system and eliminating the remaining two quarts as urine through the bladder. As with most parts of the body, however, when this system breaks down, it causes pain and discomfort. And unfortunately, it breaks down quite frequently. Urinary tract infections (UTIs), second only to respiratory infections in frequency, account for 10 million visits to the doctor each year. One in five women will suffer from cystitis, an inflammation of the bladder, at some time in her life. Twenty percent of women who have a UTI will have a second infection, and 30 percent of those will have yet another. In addition, at least 10 million adults suffer from urinary incontinence (an inability to hold urine) to some degree.

Unfortunately, the pathophysiology of many chronic disorders of the lower urinary tract disorders is poorly understood. Exceptions are bacterial infections of the bladder, venereal diseases affecting the lower urinary tract and bladder carcinomas secondary to systemic exposure to certain toxic substances. However, the most common diseases and disorders of the lower urinary tract are not satisfactorily explained by any general theories that could give rise to the development of rational methods of treatment. Those disorders and diseases include, for

example, urinary hesitancy, urinary incontinence, fibrosis of the urinary tract, urinary dribbling, urinary frequency and bladder cancer.

Urinary retention and urinary incontinence are common complaints of both men and women of advancing age. Urinary incontinence is the inability of the bladder to retain urine resulting in urine loss as a consequence of either urge (urge incontinence), or physical or mental stress (stress incontinence). Urinary incontinence (UI) is defined as an involuntary loss of urine which is objectively demonstrable and a social or hygienic problem. UI occurs in 15 to 30 % of the US population over the age of 60 years. Severe incontinence affects about 6 % of the population in general in the US with around $10 billion spent in direct costs to care for these patients. Urinary incontinence is attributed to a variety of causes including neurogenic bladder from stroke and spinal cord injury, post operative complications of abdominal and pelvic surgeries, secondary to drug effects, secondary to laxity of the pelvic ligaments with advancing age, secondary to childbirth and a host of other causes.

Though many cases of urinary incontinence do not fit a clear-cut classification, they generally fall into one of four categories of UI: urge, stress, overflow and functional incontinence. The etiology of incontinence is determined by a careful history, physical exam and by tests of urinary flow (urodynamics).

Urge incontinence is characterized by the involuntary loss of urine associated with a strong and usually urgent, and quickly irresistible desire to urinate. Either an overactive detrusor or hypersensitivity is associated with urge incontinence. In most cases, uninhibited bladder contractions are at fault. They may be a result of damage to the central nervous system from stroke or diseases such as multiple sclerosis, or may be caused by urinary infections or bladder tumors. A variant of this disorder is reflex incontinence, in which unintended urination occurs without feelings of urgency.

Stress incontinence is the loss of urine during actions that increase abdominal pressures such as lifting, laughing, coughing or exercise. The failure of bladder outlet muscles to respond to a full bladder normally causes excess urine to be lost in trickles. Stress incontinence is the most common type of UI among women. Its hallmark is the involuntary loss of urine during physical activity, sneezing or coughing. The disorder may have its roots in the unique stress that pregnancy places on the urinary tract. However, symptoms may not be noticed until menopause, when the bladder tissues start to sag due to a drop in estrogen levels. Estrogen supplements often improve the condition, but have other drawbacks. Other remedies include Kegel exercises (rhythmic flexing of the muscles surrounding the vagina, anus, and urethra), and surgery to reposition the bladder.

Overflow incontinence happens when the bladder cannot empty normally and becomes overdistended. This condition usually involves frequent, sometimes nearly constant, urine loss. Causes include neurologic abnormalities such as spinal cord injury and conditions that block outflow such as an enlarged or cancerous urinary or a stricture of the urethra.

Functional incontinence is generally related to factors other than the bladder such as being unconscious or sedated.

Treatment depends on the cause of the problem. Medications prescribed for incontinence include, for example, bladder relaxants such as propantheline (Pro-Banthine), antispasmodic drugs such as flavoxate (Urispas), dicyclomine (Bentyl), anticholinergic drugs such as oxybutynin (Ditropan), antidepressants such as imipramine (Tofranil) or beta adrenergic agonists such as pseudoephedrine. Estrogen replacement therapy is also used. Treatments for incontinence include drugs with bladder relaxant properties, i.e., which help to control bladder detrusor muscle overactivity. Such drugs are effective in 80 to 85% of patients with uninhibited bladder contractions, with anticholinergic medications representing the mainstay of this type of treatment. For example, anticholinergics such as propantheline bromide, and combination smooth muscle relaxant/anticholinergics such as racemic oxybutynin and dicyclomine, have been used to treat urge incontinence. (See, e.g., A. J. Wein, Urol. Clin. N. Am., 22:557-77 (1995).)

However, no treatment for incontinence, including existing drug therapies, has achieved complete success with all classes of incontinent patients, and without significant side effects. For example, adverse effects, such as drowsiness, dry mouth, constipation, blurred vision, headaches, and cardiac arrhythmia which are related to the anticholinergic activity of drugs such as racemic oxybutynin, occur frequently and can be sufficiently troublesome to necessitate discontinuing treatment in up to 25% of patients, depending on the dosage. Yet, despite the occurrence of unwanted anticholinergic effects in many patients, and an apparent lack of efficacy in the elderly institutionalized population, racemic oxybutynin nevertheless is considered the drug of first choice in patients with bladder detrusor muscle hyperactivity when pharmacological therapy is indicated (cf. Yarilur et al., Drugs Aging, 6:243 (1995)).

Other major urinary disorders include interstitial cystitis and bladder cancer. Cystitis is an inflammation of the urinary bladder and associated structures for which there is no universal effective treatment program (Fleischmann, J. D. et al. 1991. Journal of Urology, 146:1235). Symptoms resulting from cystitis include, but are not limited to, urgency for urination, increased frequency of urination and suprapubic pain usually relieved by voiding. Other symptoms can include, but are not limited to, arthritis, spastic colon, low grade fever and irritability. Mammals

with cystitis can be significantly disabled, and mammals with advanced cystitis can require major surgery in order to function.

Cystitis can result from, among other causes, infection, trauma, allergy, malignancy, uroliths, acute causes and undetermined causes. Infection associated cystitis includes, but is not limited to, inflammation of the urinary bladder and associated structures associated with bacterial, fungal, yeast, viral and parasitic causes. Trauma associated cystitis includes, but is not limited to, inflammation of the urinary bladder and associated structures associated with mechanical, chemical and surgical causes. Mechanical causes include, but are not limited to, cystoscopy, traumatic fibrosis, ultrasound, radiation therapy, catheterization and spinal cord damage. Surgical causes include, but are not limited to, tumor resection, cystotomy, urinary bladder ablation, urethrostomy and cystocentesis. Allergy associated cystitis includes, but is not limited to, inflammation of the urinary bladder and associated structures associated with hypersensitivity reactions and drug reactions. Acute causes of cystitis include, but are not limited to, inflammation of the urinary bladder and associated structures associated with venereal disease, irritation by a foreign body, injury and radiation therapy for cancers of the pelvic region. Malignancy associated cystitis includes, but is not limited to, inflammation of the urinary bladder and associated structures associated with cancerous growth. Undetermined causes of cystitis include, but are not limited to, inflammation of the urinary bladder and associated with interstitial cystitis. Other causes of cystitis are known to those skilled in the art and are included as cystitis.

It has been suggested that abnormalities of or deficiencies in the glycosaminoglycan layer lining the transitional epithelium of the urinary bladder may be a primary defect in cystitis. (Eldrup J. 1983. British Journal of Urology, 55:488). These abnormalities or deficiencies may enable increased permeability of the transitional epithelium (Parsons, E. L. et al. 1990. Journal of Urology, 143:690) and this increased permeability may enable urinary solutes to gain access to the subepithelial tissue and to induce an irritative, inflammatory response that contributes to the symptoms of cystitis.

There is no standard treatment for cystitis. Among the treatments used for interstitial cystitis are hydraulic distention of the urinary bladder, oral amitriptyline or sodium pentosanpolysulfate, intravesical instillation of dimethylsulfoxide, oxychlorosene sodium, silver nitrate, heparin, or a composition comprising an angiostatic steroid and pentosanpolysulfate. However, the efficacy of these treatments is variable.

Bladder cancer accounts for two to four percent of all cancers. It is most prevalent in people over age 50 and more common in men than in women. Approximately one-quarter of the

people with this disease have no early symptoms. Most, however, experience blood in the urine. Other symptoms include pain after urination; frequent urination, especially at night; and dribbling. The causes of bladder cancer are thought to include tobacco, nitrates and aniline dyes. Superficial bladder tumors can be removed surgically through the urethra by use of a cystoscope. If a tumor has penetrated the bladder wall, however, partial or even total removal of the bladder may be necessary, depending on the tumor's location.

Each known treatment for urinary disorders has limitations and drawbacks. Most of the side effects of medical treatments stem from the systemic (oral) administration of a therapeutic agent to treat a very localized problem in the lower urinary tract. The alpha-adrenergic receptor antagonists may cause a significant decrease in the systolic blood pressure, syncope, orthostatic hypotension, asthenia, dizziness, headache, sleepiness, fatigue and sexual dysfunction. A recent myocardial infarction, transient ischemic attack or cerebrovascular accident constitute relative contraindications to the use of alpha blockers. The effect of alpha-blockers is usually apparent in the first two weeks of treatment and maximum clinical effects are seen in one or two months (LM Eri et al, Drugs Aging, op cit).

The use of oral therapeutic compounds leads to exposure of all the tissues of the body in an attempt to reach the lower urinary tract. Local administration of a drug directly to lower urinary tract is hampered by the fact that these organs are internal. Doses used in systemic administration are much greater than one might otherwise need if a more direct route of administering drugs were possible. For example, the bladder and urethra constitute less than 1% of the total body mass of an average human. Thus, systemic therapy must expose 99% of the body to a pharmacologically active drug in order to reach therapeutic levels in the 1% of the body being targeted. Further, many drugs that are given orally are incompletely absorbed and extensively metabolized by the liver before entering the systemic arterial circulation. Alpha receptors are present diffusely throughout the vascular system and in other organs of mammals. Thus, drugs given to block alpha receptors in the bladder will certainly result in inhibiting normal alpha receptor mediated physiologic functions throughout a mammal. Muscarinic receptors are also present diffusely throughout a mammal and will be affected by oral administration of anti-cholinergic drugs given to treat the bladder.

A few studies report administering PGE-2 intravesicularly in women suffering from atonic bladder as a post-hysterectomy complication (see U Ulmsten "Prostaglandins and the urinary tract" Acta Obstetricia et Gynecologica Scandinavia, Supplement 1983; 113:55-8). These reports state that PGE-2 is either efficacious or without merit in hastening the normal recovery of bladder tone (see A Bergman"Prostaglandins for enhancing bladder function after

hysterectomy" J Reproductive Med 1992; 37(4):320-2). Hysterectomy patients are routinely given a urinary catheter pre-operatively since normal bladder function is consistently interrupted by the hysterectomy in the early post-operative period. The rationale for these trials was that prostaglandins are felt to be important in maintaining normal bladder tone. No consistently beneficial effects of prostaglandins were found in the treatment of post-operative bladder atony.

Administration of drugs through the penile urethra for the treatment of erectile dysfunction is described in U.S. Pat. Nos. 5,773,020; 5,474,535; 5,919,474; 5,886,039 and others. The portion of the urethra from the proximal portion of the fossa navicularis to the distal portion of the pendulous urethra is utilized in those methods of treating erectile dysfunction (see FIG. 1). Neither the prostatic urethra nor the distal portion of the penile urethra (the urethral segment) is disclosed. The use of a medicated catheter to treat local infection and irritation of the urethra and bladder are disclosed in U.S. Pat. No. 4,640,912. The trans-urethral administration of some drugs is suggested in U.S. Pat. Nos. 4,478,822; 4,610,868; 4,640,912; 4,746,508 and 5,872,107.

Prostaglandins and interferons have not been reported to be used for urinary incontinence or other urinary disorders. Indeed, several studies have implicated PGE2 in urinary hyperplasia and prostadynia.

Thus, there is a pressing need for new and improved methods, compositions and devices to prevent and treat urinary disorders in mammals. Compositions and methods of treatment that exhibit more rapid onset of action, more potent and selective effects on peak urinary flow rates, less systemic side effects, without deleterious effects upon sexual function or urinary continence are needed. Since aging is also associated with increasing incidences of heart attack and strokes, methods of treating urinary disorders that do not exacerbate cardiovascular or cerebrovascular disease are particularly needed. There is also a need for routes of administration for drugs that minimize systemic exposure. There remains a need for compositions and kits useful for preventing and treating urinary disorders in mammals.

Summary of the Invention

It is one object of the present invention to provide compositions for preventing and/or treating urinary disorders in mammals.

It is another object of the present invention to provide methods for preventing and/or treating urinary disorders in mammals.

It is another object of the present invention to provide devices to deliver therapeutic compounds to the mucosal membranes of the lower urinary tract.

It is another object of the present invention to provide kits for preventing and/or treating urinary disorders in mammals.

These objects have been obtained by the inventor's discovery that administering certain therapeutic compounds to mucosal membranes of the lower urinary tract of a mammal is effective in preventing and/or treating urinary disorders.

The present invention has demonstrated a method of treating urinary disorders with efficacy within minutes of treatment. This invention involves minimal intervention when compared to present therapies and offers hope for the prevention and/or treatment of urinary disorders.

Additional aspects, features, embodiments and advantages of the present invention will be set forth, in part, in the description that follows, or may be learned from practicing or using the present invention. The objects and advantages may be realized and attained by means or features and combinations particularly pointed out throughout this description and the appended claims. It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not to be viewed as being restrictive of the invention as claimed.

Brief Description of the Drawings

The accompanying drawings, which are incorporated in, and constitute a part of, this specification, illustrate embodiments of the present invention and, together with the description, serve to exemplify the principles of the present invention.

Fig. 1 depicts the urethra of a male.

Fig. 2 depicts the urethra of a female.

Detailed Description of the Preferred Embodiments

All patents, patent applications and publications cited in this description are incorporated herein by reference in their entirety.

In a first embodiment, the present invention provides novel compositions for the prevention and/or treatment of urinary disorders in mammals.

As used herein, "urinary disorders" refers to urinary incontinence of any etiology, urinary hesitancy, fibrosis of the urinary tract, urinary dribbling, cystitis of any etiology, urinary frequency and bladder cancer. Bladder atony is not a "urinary disorder" as used herein.

One novel composition comprises a prostaglandin compound and an interferon. Another novel composition comprises urethral suppositories with tocopherol analogs and/or vitamin C

analogs. Urethral suppositories containing verapamil in a free base form are also believed to be novel. Also believed to be novel are compositions containing an interferon, chemotherapeutic agents such as tocopherol succinate and vitamin C analogs, anti-muscarinic agents and verapamil.

In a second embodiment, the present invention provides novel methods for the prevention and/or treatment of urinary disorders in mammals comprising administration of one or more therapeutic compounds to the mucosal membrane of the lower urinary tract of the mammal.

In a preferred embodiment, the method for preventing urinary disorders comprises:

a. Identifying the population of mammals at risk of developing a urinary disorder;

b. Performing baseline testing of mammals at risk;

c. Administering one or more therapeutic compound(s) to the mucosal membrane of the lower urinary tract of the mammal; and

d. Repeating the baseline testing to evaluate the mammal's response to intervention and to determine whether subsequent interventions should be altered.

When the urinary disorder is urinary incontinence (UI), mammals at risk of UI can be identified by, for example, evaluating historical factors known to be associated with UI such as age, race, sex, family history and medical history. Since the strongest factor associated with UI is age, one may consider everyone over a certain age to be at risk of developing UI and a potential candidate for preventative therapy.

After identifying mammals with UI, baseline testing (step b) can be performed by recording patient symptomatology using a measurement device such as the Incontinence Impact Questionnaire (C Norton, Int Rehabil Med 1982; 4: 9-14). A screening urodynamics study with a minimum of peak and mean urinary flow rates can also be performed. Assessment of the urinary tract by physical exam (including measurement of the post-void residual urine remaining in the bladder) or by visualization with radiologic methods may also be used for baseline testing.

After conducting the baseline tests, one or more therapeutic compound(s) may be administered to the mucosal membrane of the lower urinary tract of the mammal (step c), preferably utilizing the least invasive method possible. For example, urethral suppositories containing (a) PGEs with or without interferons or (b) Type IV phosphodiesterase inhibitors are suitable for administration. Administration of a suitable dose of the therapeutic agent nightly or every other night is also suitable.

After completing administration of the desired dosage regimen, repeat baseline testing to evaluate the mammal's response to intervention and to determine whether subsequent interventions should be altered (step d) can optionally be carried out by re-evaluating the

baseline determinants recorded in step b at intervals of 6 months to 2 years. These determinants preferably consist of at least the symptomatology and the peak urinary flow rate. Improvement in these determinants is desirable and indicates regression of the urinary disorder. Continuation of the intervention used is preferable. One indication that the intervention used is effective is if no decrease in peak urinary flow or development of symptomatology occurs. In this case, the individual should continue the intervention and be re-evaluated in 6 month to 2 years. If worsening of the symptoms or other indicators occurs, use of higher doses of therapeutic compound(s) may be tried.

When the urinary disorder is bladder cancer, mammals at risk of developing bladder cancer can be identified by factors including, but not limited to, family history, race, age smoking history, tobacco history and occupational exposure (step a). Strongly positive family histories or pathology reports of pre-malignant changes on biopsies of bladder tissue are indications to initiate preventative therapy.

After identifying mammals at risk of developing bladder cancer, baseline testing (step b), such as urine cytologies are warranted. Available bladder biopsy reports can be studied and new bladder biopsy material obtained at the discretion of the clinician.

After performing baseline testing, one or more therapeutic compound(s) may be administered to the mucosal membrane of the lower urinary tract of the mammal (step c). For example, urethral suppositories with (a) prostaglandins with or without an interferon of the alpha or gamma subgroup or (b) tocopherols, vitamin C or retinol or their analogs are suitable for administration to the mammal. Preferably, the prostaglandin is PGA-1, PGA-2, PGJ2, Δ^{12}-PGJ-2, 15-deoxy-$\Delta^{12,14}$-PGJ-2, PGD-2 or 15-deoxy-$\Delta^{12,14}$-PGD-2. The therapeutic compound(s) can be administered nightly or every other night.

After completing the administration of the desired dosage regimen, baseline testing for bladder cancer (step d) can be accomplished, for example, by serial urine cytologies. Available bladder biopsy reports can be studied and new bladder biopsy material obtained at the discretion of the clinician.

Methods for treating urinary tract disorders preferably comprise

a. Diagnosing the mammal as having a urinary tract disorder;

b. Performing baseline testing of the mammal having a urinary tract disorder;

c. Administering one or more therapeutic compound(s) to the mucosal membrane of the lower urinary tract of the mammal; and

d. Performing baseline testing to evaluate the mammal's response to the treatment and to determine whether subsequent treatments should be altered.

Performing baseline testing of the mammal and administration of the therapeutic compound(s) are preferably accomplished by the same measures described above in connection with methods for preventing urinary tract disorders, if the condition is mild. More severe cases of urinary disorders are best treated by administration of one or more therapeutic compound(s) to the prostatic urethra as described below and in the examples. Treatment of bladder cancer may be effected by administration of chemotherapeutic agents via the prostatic urethra.

As used herein, "therapeutic compound" refers to any therapeutic compound of benefit or potential benefit to urinary disorders. Particularly preferred therapeutic compounds are selected from any of the groups listed below for which non-limiting examples are given:

I. Autocoids and Cytokines such as Prostaglandins and Interferons

II. Chemotherapeutic Agents

III. Alpha-receptor antagonists

IV. Prostaglandin dehydrogenase inhibitors

V. Phosphodiesterase inhibitors

VI. Anticholinergic/antispasmodic agents

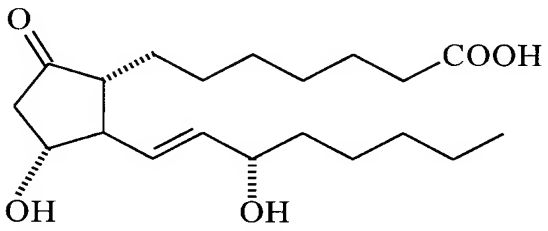
I. Cytokines

I (A). Prostaglandins

Examples of suitable prostaglandins include any natural or synthetic chemical designated to belong to a prostaglandin family, such as PGE-1; PGE-2; PGE-3; PGA-1; PGB-1; PGD-2; 15-deoxy-$\Delta^{12.14}$-PGD-2, PGE-M; PGF-M; PGH-2; PGI-2; 19-hydroxy-PGA-1; 19-hydroxy-PGB-1; PGA-2; PGB-2; 19-hydroxy-PGA-2; 19-hydroxy-PGB-2; PGB-3; 16,16-dimethyl-PGE-1 methyl ester; 15-deoxy-16-hydroxy-16-methyl-PGE-1 methyl ester; 16,16-dimethyl-PGE-2; 11-deoxy-15-methyl-PGE-1; 16-methyl-18,18,19,19-tetrahydrocarbacyclin; (16RS)-15-deoxy-16-hydroxy-16-methyl-PGE-1 methyl ester; (+)-4,5-didehydro-16-phenoxy- -te tranor-PGE-2 methyl ester; 11-deoxy-11a,16,16-trimethyl-PGE-2; (+)-11a,16a,b-dihydroxy-1,9-dioxo-1-(hydroxymethyl)-16-methyl-trans-prostene; 9-chloro-16,16-dimethyl-PGE-2; arboprostil; iloprost; CL 115,347; 16,16-dimethyl-PGE-2; 15(S)-15-methyl-PGE-2; 9-deoxy-9-methylene-16,16-dimethyl-PGE-2, potassium salt; carbaprostacyclin; prostaglandin D-2; 19(R)-hydroxy-PGE-2; 13,14-dihydro-PGE-1; 11β-PGE-2; 19(R)-hydroxy-PGE-1; 11-deoxy-16,16-dimethyl-PGE-2; PGJ-2; Δ^{12}-PGJ-2; 15-deoxy-$\Delta^{12.14}$-PGJ-2 and semisynthetic or synthetic derivatives of these natural prostaglandins. Cyclodextrin complexes are also included as they may enhance the activity of the solution and stabilize the prostaglandin. Racemic, optically enriched or purified stereoisomers of any of these compounds are also included. Physiologically acceptable salts are also included.

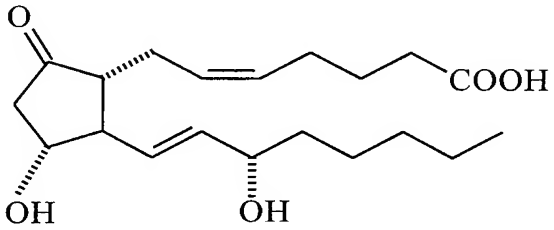
Preferably, the prostaglandin is PGE-1, PGE-2, PGE-3, misoprostol or misoprostanoic acid for the treatment and prevention of urinary disorders. Preferably, the prostaglandin is PGA-1, PGA-2, PGJ-2, Δ^{12}-PGJ-2, 15-deoxy-$\Delta^{12,14}$-PGJ-2, PGD-2 or 15-deoxy-$\Delta^{12,14}$-PGD-2 for the treatment and prevention of bladder cancer. Such prostaglandins are commercially available from Cayman Chemical, Ann Arbor MI and/or are described in Alex Gringanz, Introduction to Medicinal Chemistry, Wiley-VCH, Inc., New York, pp. 158-159 and 641-642, 1997, which is incorporated herein by reference.

PGE-1, prostaglandin E_1, is also known as alprostadil or PGE_1. The formal chemical name of PGE-1 is 3-hydroxy-2-(3-hydroxy-1-octenyl)-5-oxocyclopentaneheptanoic acid, and the structure of PGE-1 is



Prostaglandin E_1 may be isolated from sheep seminal vesicle tissue as described in Bergstrom et al., Acta. Chem. Scand., vol. 16, p. 501 (1962) and J. Biol. Chem., vol. 238, p. 3555 (1963). The synthesis of prostaglandin E_1 may be carried out as described in Corey et al., J. Am. Chem. Soc., vol. 91, p. 535 (1969); Corey et al., J. Am. Chem. Soc., vol. 92, p. 2586 (1970); Sih et al, J. Am. Chem. Soc., vol. 94, p. 3643 (1972); Sih et al., J. Am. Chem. Soc., vol. 95, p. 1676 (1973); Schaaf et al., J. Org. Chem., vol. 37, p. 2921 (1974); and Slates et al., Tetrahedron, vol. 30, p. 819 (1974).

PGE-2, prostaglandin E_2, is also known as dinoprostone or PGE_2. The formal chemical name of PGE-2 is 7-[3-hydroxy-2-(3-hydroxy-1-octenyl)-5-oxocyclopentyl]-5-heptenoic acid, and the structure of PGE-2 is:



Prostaglandin E_2 may be isolated from sheep seminal vesicle tissue as described in Bergstrom et al., Acta. Chem. Scand., vol. 16, p. 501 (1962). Prostaglandin E_2 may be synthesized as described in Corey et al., J. Am. Chem. Soc., vol. 92, p. 397 (1970); Corey et al.,

J. Am. Chem. Soc., vol. 92, p. 2586 (1970); and Heather et al., Tetrahedron Letters, p. 2313 (1973).

PGE-2 is also commercially available as a Prostin E-2 ™ suppository and as Prepidil Gel™ from Pharmacia & UpJohn Company, Kalamazoo, MI, and as Cervidil™ from Forest Pharmaceuticals, Inc., St. Louis, MO. These preparations are indicated for cervical ripening and contain between 0.5 and 20 mgs of PGE-2.

Misoprostol, also known as 15-Deoxy-16-hydroxy-16-methyl-PGE-1 methyl ester, has the formal chemical name of ( )-methyl-(1R,2R,3R)-3-hydroxy-2-[(E)-(4RS)-4-hydroxy-4-methyl-1-octenyl]-5-oxocyclopentaneheptanoate. Misoprostol (15-Deoxy-16-hydroxy-16-methyl-PGE-1 methyl ester) may be prepared as described in U.S. Pat. No. 3,965,143.

Enprostil has the formal chemical name of [1∀,2∃(1E,3R*),3∀]-7-[3-hydroxy-2-(3-hydroxy-4-phenoxy-1-butenyl)-5-oxocyclopentyl]-4,5-heptadienoic acid methyl ester. Enprostil may be prepared as described in U.S. Pat. No. 4,178,457, which is incorporated herein by reference. The free acid form of enprostil may also be used.

I (B). Interferons

Interferons are a diverse group of naturally occurring cytokines and immunomodulatory polypeptide agents. Certain interferons are known to exhibit chemotherapeutic effects against certain malignancies, immunosuppressive effects, antiviral effects or antiproliferative effects. Several of this group have been produced by recombinant technology. Interferon alpha-2b from Schering Corporation (Intron A™), interferon alpha-2a from Roche Laboratories (Roferon-A ™), interferon beta-1b from Berlex Laboratories (Betaseron™) and interferon gamma-1b (Actimmune™) from Genentech are commercially available agents.

Examples of suitable interferons for use in the present invention include interferon alpha, interferon beta or interferon gamma of natural or synthetic origin that exhibit scar lysis. Specific preferred interferons for use with this invention include any interferon that exhibits the ability to reduce or inhibit the production of fibrous connective tissue, including, but not limited to, interferons of the alpha and gamma sub-groups are preferred. Examples include interferon alpha-2a, interferon alpha-2b and interferon gamma-1b.

II. Chemotherapeutic Agents

Any available chemotherapeutic agents that show activity against carcinoma in the urinary tract may be used in the present invention. Agents that demonstrate marked irritation or toxicity to the mucosal surface are to be avoided. Several relatively innocuous agents that demonstrate in vitro activity against cancer cell cultures are readily administered by the present method such as, but not limited to, tocopherols, alpha-tocopherol succinate, vitamin C and

analogs, retinol and vitamin A analogs (C Maramag et al "Effect of vitamin C on prostate cancer cells in vitro: effect on cell number, viability and DNA synthesis" Prostate 1997 Aug 1; 32(3): 188-95).

Szarka reviews the strategy of chemoprevention as a possible method of blocking the development of cancers in humans (CF Szarka et al "Chemoprevention of cancer" Curr Probl Cancer 1994 Jan-Feb;18(1):6-79). These strategies center around the systemic administration of agents that have been shown to inhibit the growth of cancer cells in culture. The present invention makes it possible to deliver to the urinary tract sufficient amounts of tocopherols and vitamin C analogs to reach the necessary concentrations demonstrated by the in vitro studies. Systemic administration of these agents does not allow for the delivery of sufficient tissue concentrations to be effective. Concentrations of 1 – 2 millimolar for ascorbic acid (vitamin C), 0.5 millimolar for alpha-tocopherol and 10 micromolar for alpha-tocopherol succinate are necessary to demonstrate cytostatic or cytotoxic effects on cancer cell cultures. These tantalizing reports must be balanced by the observation that the minimal target tissue concentrations necessary to suppress the development of cancer cells or to kill cancer cells already present in a mammal exceed the maximum levels possible in oral administration by a factor of 10 – 20 fold for ascorbic acid and by around 7 – 10 fold for tocopherol. The most potent of these agents is alpha-tocopherol succinate, a succinic acid ester of tocopherol commonly used as a "dry" or solid form of vitamin E in supplements. Oral administration of this most potent antineoplastic agent results in undetectable levels of alpha-tocopherol succinate available systemically due to the rapid hydrolysis of this compound by ubiquitous serum and tissue esterases into alpha-tocopherol and the resultant 50 fold reduction in potency. Suppositories made in Example 9 are 45 mM in alpha-tocopherol succinate or 640 fold greater than the minimally effective concentration. No esterases separate the suppositories from cancerous lesions in the bladder. The present method may be used with any agent that exhibits inhibitory or toxic activity towards cancer cells but is tolerated by normal mucosal cells.

III. Alpha-Receptor Antagonists

Alpha-receptor antagonists including, but not limited to, prazosin, phentolamine, phenoxybenzamine, dibenzamine, doxazosin, terazosin, trimazosin, tolazoline, corynthanine, rauwolscine, tamsulosin and piperoxan, are suitable for use in the present invention.

IV. Prostaglandin Dehydrogenase Inhibitors

By the term "prostaglandin dehydrogenase inhibitor" it is meant any compound which exhibits a significant and selective inhibition of prostaglandin degrading enzyme, or 15-hydroxyprostaglandin dehydrogenase (PGDH). Two forms of 15-hydroxyprostaglandin

dehydrogenase (PGDH) are known: Type I, which is NAD^+ dependent, and Type II, which is $NADP^+$ dependent. Type I operates at a Km one order of magnitude lower than Type II and is thus more significant physiologically. Type I PGDH is described in Mak et al, Biochimica et Biophysica Acta, vol. 1035, pp. 190-196 (1990); Ensor et al, J. Lipid Mediators Cell Signalling, vol. 12, pp. 313-319 (1995); and Berry et al, Biochemical Pharmacology. vol. 32, no. 19, pp. 2863-2871 (1983), which are incorporated herein by reference. Berry et al., Tai et al., Muramatsu et al., and Mak et al. describe assays for determining enzymatic activity of Type I PGDH as well as methods for determining the degree of inhibition of this enzyme.

Type II PGDH is described in Chang, et al, Biochem. Biophys. Res. Commun., vol. 99, pp. 745-751 (1981); Jarabak, et al, Prostaglandins, vol. 18, pp. 241-246 (1979), and Lin, et al, Biochem. Biophys. Res. Commun. vol. 81, pp. 1227-1234 (1978), all of which are incorporated herein by reference.

Examples of suitable 15-hydroxyprostaglandin dehydrogenase inhibitors include, but are not limited to, oleic acid, palmitic acid, sulphasalazine and analogues thereof, 15(R)-prostaglandin E-1, 15(R)-prostaglandin E-2, and 15(R)-15-methyl prostaglandin E-2. US Pat. 6,103,765, which provides a more extensive discussion of PGDH inhibitors, is hereby incorporated in its entirety.

V. Phosphodiesterase Inhibitors

Suitable phosphodiesterase (PDE) inhibitors for use in the present invention include, but are not limited to, caffeine, aminophylline, theophylline, amrinone, milrinone, vesnarinone, vinpocetine, pemobendan, cilostamide, enoximone, peroximone, rolipram, R020-1724, zaniprast, dipyridamole, MY5445, IC-351 and sildenafil. Type IV phosphodiesterase inhibitors that selectively block the degradation of cGMP are preferred.

VI. Anticholinergic/Antispasmodic Agents

Anticholinergic agents may induce relaxation in the smooth muscles of the bladder when applied by the present method. Suitable anticholinergic agents for use in the present invention include, but are not limited to, atropine, scopolamine, glycopyrrolate, hyoscamine, tolterodine and oxybutynin. Agents that relax smooth muscle such as, but not limited to, flavoxate, dicyclomine and calcium channel blockers like verapamil are also of benefit in this method.

The isolated stereoisomers of any of the above agents may demonstrate improved selectivity of therapeutic action and are included in the scope of this invention.

Any single therapeutic compound or a combination of the above-listed compounds including combinations of different therapeutic groups may also be used in this invention, as long as the therapeutic compounds are physically compatible.

Particularly desirable combinations of therapeutic compounds are PGEs and alpha-blockers, PGEs and PGDH inhibitors, and PGEs and interferons.

In some instances, it may be advantageous to pre-treat the mammal with one or more of the therapeutic compounds followed by treatment with one or more of the therapeutic compounds. For example, pre-treatment with a PGDH inhibitor followed by treatment with PGE will enhance the efficacy of the present method. Additionally, for example, in the treatment of urinary disorders, the urethra may be treated with infusion of the prostaglandin solution for 10 – 30 minutes followed by infusion of the interferon solution.

The therapeutic compounds can be administered in any conventional form, such as a liquid, solid or gel. Examples of suitable liquids include sterile solutions, suspensions, and emulsions, including creams, ointments, and liposomes. Methods for preparing various dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed. (Easton, Pa.: Mack Publishing Company, 1990).

In the case of a solid preparation, the carrier may be any solid substance that is compatible with the drug to be administered, releases the drug upon contact with the mucosa and is not irritating to the mucosa as used. Examples of suitable solids include polyethylene glycol (PEG), polyethylene oxide and other low melting point or water-soluble polymers including fatty acid esters made into suppositories or pellets. Preferred PEG suppositories contain a PEG which is solid at ambient or room temperature but rapidly dissolves/melts when placed on the urethra. Long chained fatty acid triglycerides with or without fatty acid esters are well suited to use with this invention.

Examples of suitable gels include triacetin, hydroxycellulose, gels composed of water, propylene glycol, hydroxypropyl methylcellulose and any other gels which are compatible with the therapeutic agent(s). Liposomal mixtures are particularly preferred when one component is lipid soluble and one component is water soluble. The liposomes may be prepared as either anionic or cationic liposomes depending upon the therapeutic compound to be used. A preferred gel for use with prostaglandins is lecithin organogel prepared according to H. Willimann et al, "Lecithin organogel as matrix for transdermal transport of drugs," J. Pharm. Sci., vol. 81(9), pp. 871-874 (1992). Examples of lipophilic liquids that are particularly preferred are triacetin, tricaprin, tricaproin, tricaprylin and mixtures of various triglycerides.

One may also use a gel in which one or more of the therapeutic compounds is released in a controlled-released manner (i.e., released over time) to prolong the effect of the composition. For example, PGE can be formulated into a cross-linked polyethylene oxide/urethane polymer which is well tolerated by living tissues and releases the prostaglandin in a controlled release

manner. Controlled release compositions are disclosed in D. H. Lewis, Controlled Release of Pesticides and Pharmaceuticals, Plenum Press, New York, 1981; and A. F. Kydonieus, Controlled Release Technologies: Methods, Theory, and Applications, CRC Press, Boca Raton, 1980, which are incorporated herein by reference.

Cyclodextrin complexes of some therapeutic compounds that are lipid soluble may also be used in order to increase the efficacy. For example, cyclodextrin complexes may be prepared by adding the proper stoichiometric ratio of the prostaglandin or other agent to the cyclodextrin in an aqueous solvent and then either using as is or lyophilizing to provide a solid clathrate for mixing. These complexes are described in Yamamura et al, J. Chromatogr. vol. 331, pp. 383-388 (1985); Hirayama et al, Chem. Pharm. Bull., vol. 32 pp. 4237-4240 (1984); Uekama et al, J. Pharm. Sci., vol. 73, pp. 382-384 (1984); and Yamamura et al, J. Chromatogr., vol. 303, pp. 165-172 (1984), which are incorporated herein by reference.

Matrix component(s) that are suitable for use in combination with the therapeutic compound(s) may be composed of any material or mixture of materials that is compatible with the therapeutic compound(s) and that releases the therapeutic compound(s) upon insertion into the meatus or urethra. Specific examples of suitable materials for use as matrix components include, but are not limited to, fatty acid esters, such as ethyl stearate, methyl stearate, isopropyl stearate, butyl stearate, and cetyl lactate; fatty acid ethers, such as laureth 9; cholesterol esters, such as cholesteryl oleate and cholesteryl palmitate; cholesterol ethers; fatty acid diglycerides; fatty acid triglycerides; fatty acids; phospholipids; glycolipids; and sphingolipids. Ethyl stearate and a mixture of methyl palmitate and tripalmitin are particularly preferred compounds for use as matrix components. Another example of a material suitable for use as a matrix component(s) includes materials such as hydrogels which contain or are saturated with the therapeutic agent(s).

The composition comprising the therapeutic compound(s) of the present invention may be applied by any mode of administration allowing for contact between the composition and the mucosal membranes of the lower urinary tract of a mammal, including, but not limited to, application by way of a catheter, a medicated ring, suppository, dropper, syringe, applicator, tube or by spray. When the composition is a liquid, the administration may be accomplished by means of a dropper, syringe or catheter. When the composition is in the form of a gel, lotion, or cream the administration may be carried out by means of a tube, syringe or catheter. Pharmaceutical compositions that contain the therapeutic compound(s) and are in the form of a solid may be administered by inserting the appropriate amount of the solid dose form directly into the urethra or by use of an applicator.

A particularly preferred route of administration is by application directly to the mucosa of the urethra. As shown in FIG. 1, the male penile urethra consists of three segments: the bulbar urethra, the "trans-urethral" area and the meatal segment. The term urethral administration as used herein refers to the administration of agents to any portion of the urethra from its origin at the sphincter of the bladder to the external meatus of either males or females. The depth of insertion of the suppository in urethral administration is, as measured from the external opening of the penis, generally between 2 mm and 30 mm depending on individual differences. Insertion of a meatal suppository can be easily and painlessly done by simply pressing the end of the suppository into the meatal opening of the penis. No cumbersome devices are required. In females, urethral administration is likewise easily accomplished by inserting the suppository through the external meatus (see FIG. 2). Depth of insertion in females may vary up to 30 – 40 mm. It is also possible in females to insert a urethral suppository deep enough to administer therapeutic agents to the mucosa of the bladder. Those suppositories containing a matrix material that does not melt or dissolve upon insertion are preferably inserted into the urethra to a depth which leaves a portion of the suppository protruding from the urethra, left in the urethra until the desired effect is achieved, and then removed from the urethra by means of the protruding portion.

For example, the therapeutic compounds of the present invention may be administered to the mucosal membranes of the urethra by insertion of a small gauge pediatric catheter through the external meatus into the urethra. Gentle inflation of the distal bulb of the catheter affects occlusion of the urethra and affords a direct route via the central channel of the catheter to the urethral mucosa. Infusion of the urethra with the therapeutic compound (in the form of a solution) is readily performed by retrograde injection of the solution through the tip of the catheter. Contact is maintained with the urethra by clamping the catheter to prevent the therapeutic solution from refluxing through the bore of the catheter and by the inflated catheter bulb preventing the drug solution from draining down the urethra. The sphincter of the bladder prevents spillage of the drugs into the bladder. Volumes of 0.5 – 1.5 ml solution are well tolerated without leakage of the drug around the inflated bulb of the catheter. Provision for monitoring the pressure in the area of the urethra being treated is made by placing the sensing tip of a pressure transducer into that area through the catheter. This route is quite distinct from the "trans-urethral route" reported by Place in U.S. Pat. Nos. 5,773,020 and 5,919,474 and does not result in undesired side effects such as penile erection in males. Contact time may vary between 30 –180 minutes. The catheter bulb is deflated at the end of the treatment period and the catheter removed. This method is very well tolerated in an outpatient setting and no adverse effects have

been seen to date. A number of 3 way catheters are commercially available and may be utilized within the scope of this invention.

In a third emodiment, the present invention also provides novel devices for the administration of therapeutic compound(s) to the mucosal membranes of the lower urinary tract. Such devices are constructed of a drug reservoir means that in its simplest form is a ring of material containing the therapeutic compound that is placed in the urethra. This medicated ring consists of an outer ring of material in direct contact with the urethral mucosa. This direct contact facilitates drug delivery to the urethra. A central tubular means allows uninterrupted flow of urine from the bladder.

The ring may be made out of any material that allows release of the drug components, including, but not limited to, hydrogels, high melting triglycerides, polyethylene glycols and polyethylene oxides. Materials that allow timed-release of the therapeutic compound such as a hydrogel are preferred. The ring may be made of a bioerodable material that releases the therapeutic compound as the matrix is eroded or other release mechanisms such as an osmotic pillow that swells upon insertion as it absorbs water from the urethra causing release of a solution of the therapeutic compound(s) through controlled diameter apertures or openings in the outside of the ring. Precautions necessary to prevent the hydrogel from swelling and causing obstruction to the flow of urine include limiting the thickness of the hydrogel ring that is placed in the urethra. Alternatively, a ring composed of methyl palmitate and tripalmitin allows timed-release of the therapeutic compounds without swelling. Provisions may be made for retrieval of the ring should it be necessary due to side-effects in a patient or to terminate the effects (by a means to remove such as a string). Alternatively, the ring may be made to adhere to the outer surface of a urinary catheter in the region that will be in contact with the urethra. Such a catheter may be inserted into the bladder and left in place to continuously release the therapeutic compounds into the urethra for as long as several days.

Another variation of this invention is a double lumen catheter device. One lumen would be continuous with the urinary bladder in order to drain urine as it forms. The second lumen would be connected to a pump and drug reservoir on one end and to a fenestrated or multi-channeled opening on the outside of the catheter in contact with the urethra. This arrangement allows great latitude in controlling dosing and exposure of the mucosa of the urethra to the therapeutic compounds. This arrangement would be of greatest value in the treatment of cancers and severe cases of urinary disorders.

The glans penis is derived embryologically from the same tissue as the meatal urethra and is normally covered by the foreskin. Thus, the glans penis may be considered an extension

of the distal urethra for the purpose of this invention. Similarly, the clitoris and surrounding tissues are the female homologues of the glans penis in the male. Application of the therapeutic agents to these tissues in the female should be considered an extension of the distal urethra for the purpose of this invention. Meatal application of the composition for the purposes of this invention involves application of the therapeutic agents directly to the most distal or meatal urethra whether the mammal is male or female. Meatal application of the therapeutic agents may also be achieved by casting the therapeutic agents into a suppository and dispensing the suppository to a patient for use at home. Inserting a suppository trans-meatally is effective in delivering the therapeutic compounds to the urinary bladder. This surprising and totally unexpected result affords a novel route of administering therapeutic compounds to the urinary tract via a minimally invasive procedure.

The preferred method of administration will depend upon whether the goal of treatment is to prevent or to treat a urinary disorder and upon the severity of the urinary disorder. Preferably, for the prevention of urinary disorders the therapeutic compound(s) is administered by the trans-meatal route, for example with a suppository. Suitable candidates for preventative treatment will be patients who have a strong family history of urinary disorders, patients with early evidence of a progressive decline in the maximum urinary flow rate, patients with early symptoms of a urinary disorder and any individual over the age of 60 in which the treatment is well tolerated. Meatal suppositories may be dispensed for home use making this route ideal for the administration of therapeutic compounds with minimal expense and intrusion into the patient's life.

In one preferred embodiment, the suppository has a round or pointed tip to facilitate entry into the urethra. Alternatively, the suppository may be tapered along all of or at least a substantial part of its length. The base of the suppository may be distended or flared to provide a built-in stop, so that the depth of the insertion may be determined by the length from the tip of the suppository to the beginning of the flare. Alternatively, the base of the suppository may be attached to a piece of foil, plastic or paper or attached to the inside of the tip of a condom (for use in males) in order to set the depth of insertion.

Suppositories for use in connection with the present invention will typically have a cross-section having a maximum dimension of from about 1 mm to about 25 mm, preferably from about 2 mm to about 10 mm, most preferably from about 2 mm to about 6 mm, along the portion of the suppository intended to be inserted into the urethra. Although there is in principal no lower limit on the minimum cross-sectional dimension along the portion of the suppository intended to be inserted into the urethra, practically speaking, the suppository should be thick

enough to retain sufficient structural integrity to permit insertion of the suppository into the urethra without breaking or significantly bending the suppository. As noted above, the present suppository may have a shape in which the base of the suppository is distended or flared. The distended or flared portion of the suppository will typically have a minimum dimension of at least about 5 mm, preferably at least about 10 mm. Although there is in principal no upper limit on the maximum cross-sectional dimension of the distended or flared portion of the suppository, practically speaking, it is not necessary to make the distended or flared portion any larger than what is required to prevent insertion of the suppository into the urethra beyond the point at which the distended or flared portion begins.

For the treatment of urinary disorders with mild or moderate severity of symptoms, the trans-meatal route is preferable. More severe symptomatology or a desire to see more rapid therapeutic effects would make the route utilizing the urethra preferable. Administration of therapeutic compounds with a narrow therapeutic index may be most safely administered via the urethra under the direct supervision of the physician.

The amount of therapeutic compound(s) to be administered will depend upon the exact size and condition of the patient, severity of the urinary disorder and the specific composition and method being used. The therapeutic compounds of the present invention are to administered in a therapeutically effective amount, which is understood to mean a nontoxic but sufficient amount of the drug or agent to provide the desired effect. For example, an effective amount means the amount that results in improvement in symptom scores or that results in improvement in peak urinary flow rates or other indices used to monitor the urinary disorder. A therapeutically effective amount in bladder cancer means the amount that results in reduction in bladder tumor mass, improvement in urine cytologies or improvement in bladder biopsy specimens.

For example, if the therapeutic compound is a prostaglandin, although the exact amount to be administered will depend on the exact size and condition of the patient and severity of the disorder, the prostaglandin is suitably administered in an amount of from 1 nanogram to 1,400 micrograms, preferably from 1 microgram to 1,000 micrograms, most preferably from 10 to 500 micrograms. Good results have been obtained with prostaglandin E concentrations in the 100 – 1,000 mcg per ml range. The broad ranges of suitable dosages reflect clinical findings that various co-agents and carriers can either increase or decrease the drug activity exhibited by a given mixture and that individuals may exhibit different levels of sensitivity to a therapeutic agent. In practice, one would begin with a small dose of a therapeutic agent to ascertain the minimum dose needed for an adequate clinical response and increase doses if needed.

The duration of treatment and time period of administration of the therapeutic agent will also vary according to the size and condition of the patient, the severity of the illness and the specific composition and method being used. For example, typically, the prostaglandin will be administered for 30 – 90 minutes when a catheter based device is used for treatment in a physician's office; for 2 – 72 hours when a controlled release device is used; and, for several hours when a trans-meatal suppository is used. The administration of the trans-meatal suppository will be terminated by urination. Improvement is surprisingly and unexpectedly rapid with dramatic benefits often seen at the end of one treatment. The number of treatments to be given will depend upon the condition being treated, the severity of the condition and the response of the individual.

If the therapeutic compounds are interferons administered in combination with the prostaglandin, the amount of interferon is suitably administered from 100 – 50,000,000 IU, preferably from 1,000 – 10,000,000 IU, most preferably from 100,000 – 2,000,000 per ml. Although the exact amount of interferon to be administered will depend on the exact size and condition of the patient, good results have been obtained by administration of interferon in the range of 100,000 – 2,000,000 IU per ml. The corresponding prostaglandin dose is as described above.

Typically, a composition comprising prostaglandin and interferon will be administered for 30 – 90 minutes when a catheter based device is used; for 2 – 72 hours when a controlled release device is used; and, for several hours when a trans-meatal suppository is used. The administration of the trans-meatal suppository will often be terminated by urination.

In addition to the therapeutic compound(s) discussed above, the composition administered to the mucosal membrane will typically contain one or more pharmaceutically acceptable carriers (also termed "excipients" or "vehicles") suited to the particular type of formulation, i.e., gel, ointment, suppository, or the like. The vehicles are comprised of materials of naturally occurring or synthetic origin that do not adversely affect the therapeutic compound(s) or other components of the formulation. Suitable carriers for use herein include water, silicone, waxes, petroleum jelly, polyethylene glycol, propylene glycol, liposomes, sugars such as mannitol and lactose, and a variety of other materials, depending, again, on the specific type of formulation used.

It may in some cases be desirable or necessary to include a detergent in the formulation, in an amount effective to increase solubility of the therapeutic compound in the vehicle and bioavailability of the compound following administration. The detergent will typically be a nonionic, anionic, cationic or amphoteric surfactant. In the practice of the invention, the

surfactant is selected such that local irritation at the site of administration is avoided. Examples of suitable surfactants include Tergitol.RTM. and Triton.RTM. surfactants (Union Carbide Chemicals and Plastics, Danbury, Conn.), polyoxyethylenesorbitans, e.g., TWEEN.RTM. surfactants (Atlas Chemical Industries, Wilmington, Del.), and pharmaceutically acceptable fatty acid esters such as lauryl sulfate and the like.

The formulations may also optionally include one or more components to enhance permeation of the therapeutic compound(s), i.e., "permeation enhancers." Suitable permeation enhancers include those generally useful in conjunction with topical, transdermal or transmucosal drug delivery. Examples of suitable permeation enhancers include dimethylsulfoxide ("DMSO"), dimethyl formamide ("DMF"), N,N-dimethylacetamide ("DMA"), decylmethylsulfoxide ("C.sub.10 MSO"), polyethylene glycol monolaurate ("PEGML"), glycerol monolaurate, lecithin, the 1-substituted azacycloheptan-2-ones, particularly 1-n-dodecylcyclazacycloheptan-2-one (available under the trademark Azone.RTM. from Nelson Research & Development Co., Irvine, Calif.), lower alkanols (e.g., ethanol), SEPA.RTM. (available from Macrochem Co., Lexington, Mass.), and surfactants, including, for example, Tergitol.RTM., Nonoxynol-9.RTM. and TWEEN-80.RTM.

In a fourth embodiment, the present invention provides kits to administer therapeutic compounds and novel compositions to the mucosal membranes of the lower urinary tract for the treatment and/or prevention of urinary disorders in mammals. The kits are characterized as containing: (a) a means for containing a therapeutic compound or composition comprising a therapeutic compound and (b) a means for administering the compound or composition to the mucosal membranes of the lower urinary tract of a mammal. When the composition or compound is in the form of a suppository, the means for containing the compound or composition may be foil or plastic wrappers surrounding the suppositories that may be placed into a box or carton or other sealed container. The means for containing the compound or composition may be a bottle, canister or plastic tube when the composition is in the form of a liquid, gel, lotion or cream. Rings or catheters containing the compositions may be placed in individual foil or plastic wrappers and then placed into a box or carton. The means for administering the compound or composition may be a catheter, a medicated ring, suppository, dropper, syringe, applicator, tube or by spray. When the composition is a liquid, the administration may be accomplished by means of a dropper, syringe, catheter or finger tip. When the composition is in the form of a gel, lotion, or cream the administration may be carried out by means of a tube, dropper, syringe, catheter or finger tip. Pharmaceutical compositions that contain the therapeutic compound(s) and are in the form of a solid may be administered by

inserting the appropriate amount of the solid dose form directly into the urethra, by the use of an applicator or by the finger tip.

It is to be understood that the means for administering the pharmaceutical composition may be connected to or a part of the means for containing the pharmaceutical composition comprising.

Examples of preferred kits include:

A. A kit which includes a container which can hold 1 to 100 unit doses of the compound or pharmaceutical composition and a dropper which can dispense between 0.1 to 1.0 ml as a unit dose. The container is preferably glass, metal or a plastic known not to adsorb hydrophobic compounds.

B. A kit which includes a container which can hold 1 to 100 unit doses of the compound or pharmaceutical composition with an applicator to administer the pharmaceutical composition internally onto the mucosal surface. The container is preferably glass, metal or a plastic known not to adsorb hydrophobic compounds.

C. A kit which includes a tube which holds 1 to 100 unit doses of a compound or pharmaceutical composition, which is in the form of a cream or gel, and an applicator which can dispense a unit dose of the composition.

D. A kit which includes 1 to 100 unit doses of pellets, film or suppositories along with directions for use.

E. A kit which includes 1 to 100 unit doses of urethral rings or catheter devices for administration of the pharmaceutical composition into the urethra.

The present kits will also typically include means for packaging the container means and the administering means. Such packaging means may take the form of a cardboard or paper box, a plastic or foil pouch, etc. The present kits will also usually include written instructions that describe how to administer the therapeutic compound or pharmaceutical composition containing the therapeutic compound to the mucosa. It is to be understood that the written instructions may be on any of the container means, the administering means, or the packaging means, in addition to being present on a separate piece of paper.

Other features of the present invention will become apparent in the course of the following description of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

Examples

The present invention will be further illustrated in the following, non-limiting Examples. The Examples are illustrative only and do not limit the claimed invention regarding the materials, conditions, process parameters and the like recited herein.

I. Exemplary Formulations:

A matrix material for meatal suppositories composed of 12 – 40 % by weight of tripalmitin in methyl palmitate makes a versatile carrier for the therapeutic compound(s) in this method. A meatal suppository may be easily formed by combining 20 grams of tripalmitin with 80 grams of methyl palmitate and melting at 80° C. Lipophillic therapeutic compounds may simply be added to this melted matrix material with stirring and then cast into suppositories by any standard method. Therapeutic compounds that are not lipid soluble may be added in a volatile solvent such as ethanol with stirring and rapidly cast into suppositories. Residual alcohol is removed by application of a vacuum to the solid suppository. Solvents such as 1,2 propanediol may be added to the matrix material to increase the solubility of the therapeutic compound and left as a component of the final product. The co-solvent or volatile solvent to be used may be found by experimenting or by consulting references regarding chemical solubility of a therapeutic compound.

Matrix material with higher proportions of tripalmitin (above 20 %) exhibit delayed drug release properties. By the method above, delayed release devices for urethral administration may be easily cast.

In a preferred embodiment, the matrix component is a material or mixture of materials that results in the final composition having a melting point ranging from about 70° F to about 100° F, preferably from about 70° F to about 90° F.

Example 1

A base matrix was formed by melting 0.760 grams of tripalmitin and 3.240 grams of methyl palmitate at 80 °C with stirring. This 18 % tripalmitin matrix melts and releases any contained therapeutic agent on contact with the warmth of the urethra.

Example 2

To 4.000 grams of the molten matrix from Example 1 was added 4.0 milligrams of PGE-2 with stirring. The solution was drawn into a 2.1 mm diameter rigid tube made of high density polyethylene and allowed to cool to room temperature. One hundred unit doses containing 40 micrograms of PGE2 resulted from cutting the tubing at 12 mm lengths. The outer sleeve of polyethylene was left in place to add strength to the soft meatal suppositories. The suppository is pushed out of one end of the protective sleeve and inserted by hand to use. Any standard method

of casting suppositories may also be used. This technique works well with any prostaglandin or other lipid soluble therapeutic compound.

Example 3

To the molten mixture of Example 2 containing tripalmitin, methyl palmitate and PGE-2 was added the dry powder from one vial of 25 million IU Intron A™ with rapid stirring. This suspension is rapidly cast into suppositories as in Example 1. One hundred unit doses containing 40 micrograms of PGE-2 and 250,000 IU interferon alpha –2b are thus made. The PGE-2 is rapidly released from the matrix. The solid particles containing interferon alpha-2b are then released by the melting matrix and will slowly dissolve in the moisture of the urinary tract. This simple preparation thus enables the release of the PGE-2 dissolved in the matrix first followed by the suspended interferon particles without the use of a catheter and sequential infusions. The same result may be obtained with any lipid insoluble therapeutic agent that is a solid at room temperature. One may also use the pure interferon powder if available or may substitute a dried liposomal preparation of the therapeutic agent in this method with excellent results. This preferred embodiment may be administered at home by the patient or may be cast as a ring around a catheter by allowing the suspension to cool and solidify around that portion of a catheter that will be in contact with the urethra.

Example 4

To the molten mixture in Example 1 was added 15 milligrams of prazosin hydrochloride dissolved in ethanol with stirring. The solution was rapidly cast and produced one hundred unit doses containing 150 milligrams of prazosin hydrochloride. The residual ethanol was removed from the suppositories after solidification by vacuum. Any therapeutic agent that is not lipid soluble may be cast into suppositories by selection of a suitable volatile solvent.

Example 5

To a molten mixture 1 gram of tripalmitin and 3 grams of methyl palmitate was added 200 milligrams of oleic acid and 200 milligrams of palmitic acid with stirring until all were dissolved. Casting yielded 100 suppositories containing 2.0 milligrams each of oleic acid and palmitic acid. Similar preparations made be made with one or a combination of fatty acids. This preparation releases PGDH inhibitors into the urethra.

Example 6

Verapamil hydrochloride was dissolved in water and sodium hydroxide solution added until pH 10. The liberated free base verapamil was extracted with chloroform, The chloroform extract was dried over molecular sieves and evaporated to give the pale yellow liquid free base Verapamil. To the molten matrix in Example 1 was added 75 milligrams of Verapamil with

stirring and cast to yield one hundred suppositories containing 750 micrograms of Verapamil each. This free base form of Verapamil is absorbed much more rapidly than the available hydrochloride salt from the mucosa of the lower urinary tract. Many therapeutic agents are made into such salts for oral administration. The present invention is best used with either the free base or the free acid form of such agents since the un-ionized form is absorbed more rapidly from a mucosal surface. The alpha blockers and many anti-cholinergic agents listed above may be incorporated by this method.

Example 7

Five milligrams of either tolterodine, oxybutynin, or doxazosin prepared in a free base form as generally described in Example 6 are added in the minimal amount of ethanol to the molten matrix of Example 1 with stirring and cast into one hundred suppositories. The ethanol is removed by vacuum to give unit doses of 50 micrograms of the therapeutic agent.

Example 8

To 4 grams of the molten matrix from Example 1 was added 10 milligrams of free base sildenafil in chloroform with stirring and the mixture was rapidly cast. Removal of solvent gave one hundred suppositories containing 100 microgram doses of sildenafil.

Example 9

To 4 grams of the molten matrix from Example 1 was added 20 milligrams of ascorbyl palmitate and 100 milligrams of alpha-tocopherol succinate in ethanol with stirring and the mixture cast and placed in vacuo to give one hundred suppositories containing 0.2 and 1.0 milligrams respectively of the therapeutic agents.

Example 10

The formulations of Examples 2 - 9 may be made by substituting triacetin for the solid matrix material. The resultant liquid preparations may be instilled into the urethra or applied topically to the glans penis or clitoral area.

Example 11

The formulations of Examples 2 - 9 may be made by substituting a matrix of 30 % tripalmitin and 70 % methyl palmitate in order to afford preparations with delayed release properties.

Example 12

The formulations of Examples 2 - 9 may be made as liposomal preparations as a substitute for the solid matrix. These rapidly bioavailable preparations may be used on any mucosal surface of the urinary tract but will be particularly potent when infused into the urethra.

II. Subjective Examples:

Example 13

A 46-year-old male with no history of urinary disorders demonstrated a peak urinary flow rate of 20 ml/sec. Insertion of a Verapamil suppository from Example 6 into the meatal urethra was asymptomatic. Repeat urodynamics 15 minutes later showed a peak flow rate of 27 ml/sec – an increase of ~ 30% indicating the marked rapidity of action that the present invention affords. This example illustrates that the present invention may be used to provide an acute and localized effect on urination.

Example 14

A male or female suffering from urinary disorders may insert preparations from Examples 1 – 12 into the meatal urethra in order to obtain acute relief from the disorder.

Example 15

A male or female suffering from urinary disorders may administer preparations from Examples 10 and 12 topically to the clitoris or the glans penis in order to obtain acute relief from the disorder.

Example 16

A male or female suffering from urinary disorders may insert preparations from Examples 1 – 12 on a regular schedule into the meatal urethra in order to obtain chronic relief from the disorder.

Example 17

A male or female suffering from urinary disorders may administer preparations from Examples 10 and 12 topically to the clitoris or the glans penis in order to obtain chronic relief from the disorder.

CLAIMS

1. A method for preventing and treating urinary disorders in a mammal comprising administering to the mucusal membranes of the lower urinary tract of the mammal a therapeutically effective amount of a therapeutic compound.

2. The method of claim 1, wherein the therapeutic compound is one or more compounds selected from the group consisting of autocoids, cytokines, chemotherapeutic agents, alpha-receptor antagonists, prostaglandin dehydrogenase inhibitors, phosphodiesterase inhibitors, anticholinergic and antispasmodic agents.

3. The method of claim 1, wherein the therapeutic compound is a prostaglandin and an interferon.

4. The method of claim 3, wherein the prostaglandin is PGE-1, PGE-2, PGE-3, misoprostol, misoprostanoic acid, PGA-1, PGA-2, PGJ2, Δ12-PGJ-2, 15-deoxy-Δ12,14-PGJ-2, PGD-2 or 15-deoxy-Δ12,14-PGD-2.

5. The method of claim 3, wherein the interferon is interferon alpha-2a, interferon alpha-2b or interferon gamma-1b.

6. The method of claim 1, wherein the therapeutic compound is a prostaglandin E compound and an alpha-receptor antagonist.

7. The method of claim 1, wherein the therapeutic compound is a prostaglandin E compound and prostaglandin dehydrogenase inhibitor.

8. The method of claim 2, wherein the therapeutic compound is a chemotherapeutic agent selected from the group consisting of tocopherol, alpha-tocopherol succinate, vitamin C and analogs thereof, retinol and vitamin A analogs.

9. The method of claim 1, wherein the therapeutic compound is selected from the group consisting of an anti-muscarinic agent and verapamil.

10. The method of claim 1, wherein the therapeutic compound is administered directly to the mucosa of the urethra.

11. The method of claim 10, wherein the therapeutic compound is administered directly to the mucosa of the urethra by way of a catheter.

12. The method of claim 1, wherein the therapeutic compound is administered to the meatal portion of the urethra.

13. The method of claim 1, wherein the therapeutic compound is administered by a drug reservoir means.

14. The method of claim 1, wherein the therapeutic compound is administered by a catheter.

15. The method of claim 1, wherein the therapeutic compound is administered by a suppository.

16. A composition comprising a prostaglandin compound and an interferon.

17. A composition in the form of a suppository comprising tocopherol analogs.

18. A composition in the form of a suppository comprising vitamin C analogs.

19. A device for the administration of a therapeutic compound to the mucosal membranes of the lower urinary tract of a mammal comprising a drug reservoir means containing the therapeutic compound for insertion into the urethra.

20. The device of claim 19, wherein the drug reservoir means comprises a medicated ring comprising

a. an outer ring of material that is in contact with the urethral mucosa, and

b. a central tubular means allowing uninterrupted flow of urine from the bladder to the urethra.

Figure 1

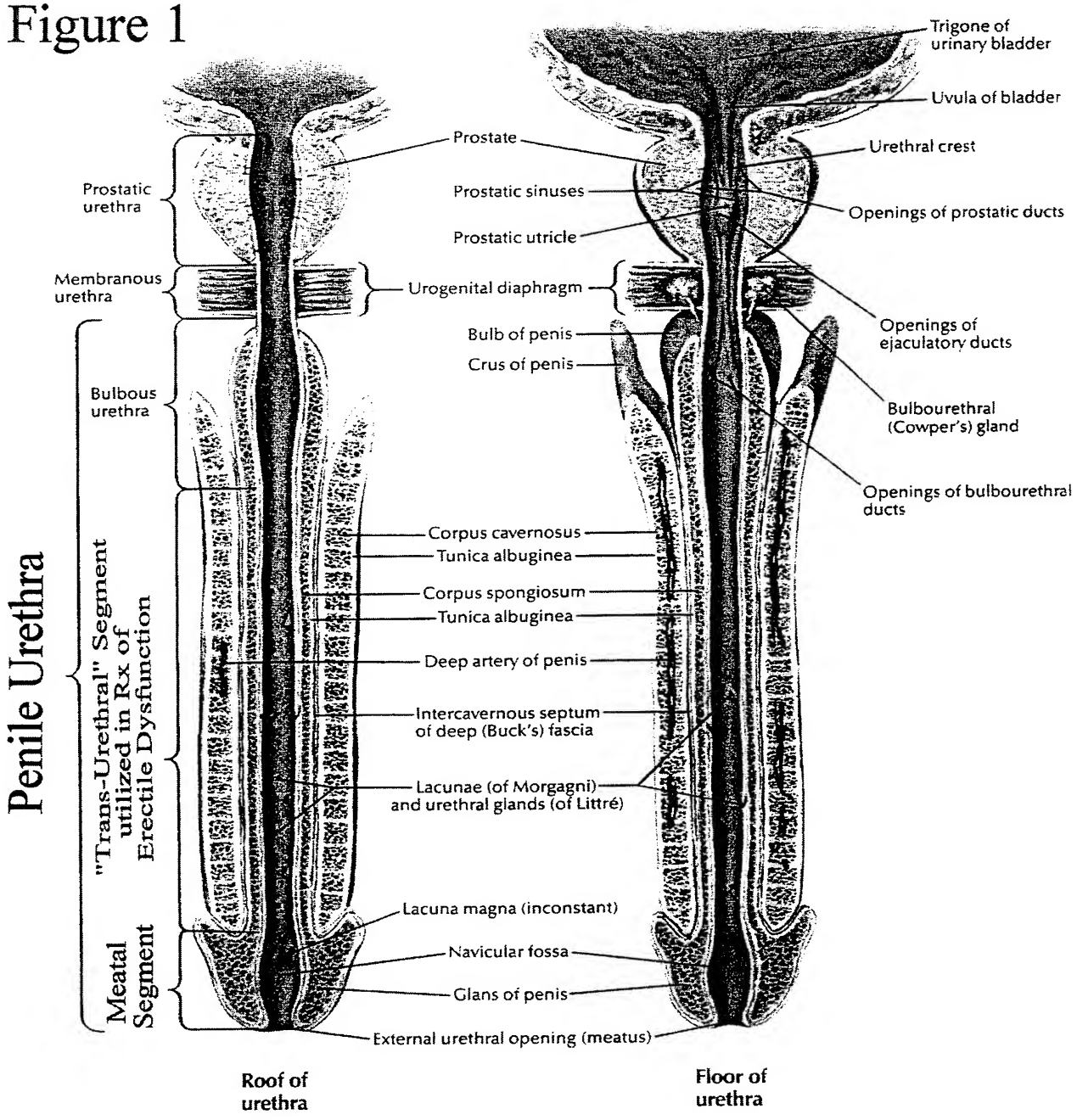
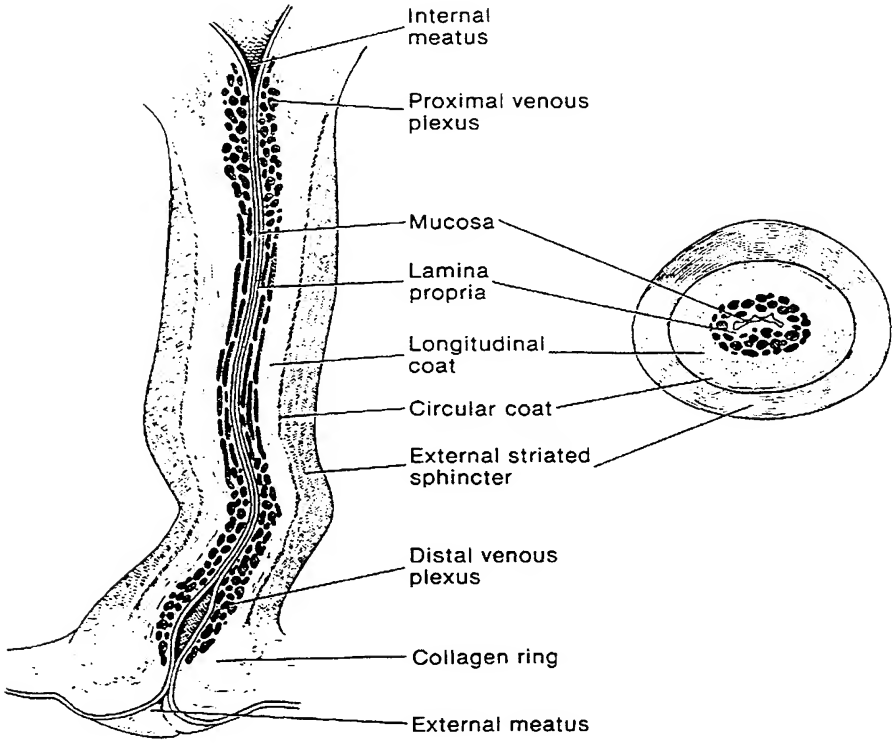

Penile Urethra
"Trans-Urethral" Segment utilized in Rx of Erectile Dysfunction
Meatal Segment
Prostatic urethra
Membranous urethra
Bulbous urethra
Prostate
Prostatic sinuses
Prostatic utricle
Urogenital diaphragm
Bulb of penis
Crus of penis
Corpus cavernosus
Tunica albuginea
Corpus spongiosum
Tunica albuginea
Deep artery of penis
Intercavernous septum of deep (Buck's) fascia
Lacunae (of Morgagni) and urethral glands (of Littré)
Lacuna magna (inconstant)
Navicular fossa
Glans of penis
External urethral opening (meatus)
Trigone of urinary bladder
Uvula of bladder
Urethral crest
Openings of prostatic ducts
Openings of ejaculatory ducts
Bulbourethral (Cowper's) gland
Openings of bulbourethral ducts
Roof of urethra
Floor of urethra

Figure 2


URETHRAL STRUCTURE
Internal meatus
Proximal venous plexus
Mucosa
Lamina propria
Longitudinal coat
Circular coat
External striated sphincter
Distal venous plexus
Collagen ring
External meatus